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Exploration of the possible effect on survival of lead-time associated with implementation of cancer patient pathways among symptomatic first-time cancer patients in Denmark

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ABSTRACT

Background: Implementation of standardised cancer patient pathways (CPPs) has provided faster diagnosis of cancer. Cancer survival has improved during the same time period. Concern has been raised that the faster diagnosis may have introduced lead-time bias by elongating the period from diagnosis to death.

Aim: We aimed to analyse the possible effect of lead time on survival due to expedited cancer diagnosis after the implementation of national CPPs among incident cancer patients diagnosed through Danish primary care.

Material and methods: We used actual observed differences in diagnostic intervals to estimate the lead-time effect. We used data from sub-cohorts from the Danish Cancer in Primary Care (CaP) cohort of first-time cancer patients: *before* and *after* CPP implementation. To calculate differences in absolute survival, we estimated the survival function after advancing the date of diagnosis in the before cohort to an earlier point in time and hereby adjusting for lead time for nine cancer types and all combined by using Kaplan-Meier analysis.

Results: Advancing the date of diagnosis implied that the absolute one-year survival increased from 68.5% to 69.4%. This accounted for 13% of the observed differences in absolute one-year survival from before to after CPPs.

Conclusion: The lead time caused by shorter diagnostic intervals after implementation of Cancer Patient Pathways seems to explain less than 15% of the observed changes in the one-year survival estimates for cancer patients in Denmark.

1. Introduction

Cancer survival varies between countries [1–4]. The survival appears to be lower in countries where general practitioners (GPs) hold the role as first point of contact to the health services and gatekeeper to specialised cancer care [3,5,6]. Many countries have sought to support GPs and increase the cancer survival by implementing comprehensive national cancer guidelines, such as the English *NICE Guidelines*, the Scottish *SIGN Guidelines* and the Danish *Cancer Patient Pathways* (CPPs) [7–15]. Even though the contents of these guidelines differ, they all operate with a guaranteed time frame for timely diagnosis under the assumption that a more timely diagnosis ultimately will improve the prognosis for cancer patients.

The implementation of CPPs has provided more timely diagnosis and treatment of cancer patients [11,16–18]. During the same time period, cancer survival has improved in Denmark and many other countries [1–3,19]. The shorter time to diagnosis may thus be assumed to have increased the survival, as recent evidence suggest [20–23]. Likewise, this may also partly explain why countries that have implemented CPPs seem to experience larger increases in the survival [2,19].

Yet, concern has been raised that faster diagnosis may introduce lead-time bias by elongating the period from diagnosis to death [24–27]. The findings of increased survival after CPP implementation could thus be explained by a lead-time effect originating from advancing the date of diagnosis to an earlier point in time without

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postponing the patient's time of death [24] suggesting an illusory benefit of CPP implementation on survival.

The aim of this study was to analyse the possible effect of lead time caused by expedited cancer diagnosis after implementation of standardised CPPs on survival among incident cancer patients diagnosed through primary care.

2. Material and methods

We compared survival rates between the first (CaP1) and the last (CaP3) sub-cohort of the Danish Cancer in Primary Care (CaP) cohort, which consists of newly diagnosed first-time cancer patients, from before and after CPP implementation [28]. We aimed to disclose the impact of lead-time bias in these two cohorts by using the methods previously used to obtain differences in the time to diagnosis, [16] and thereby applying real observed time intervals in the calculation.

2.1. Setting

The study took place in Denmark, where the publicly funded healthcare system ensures free access to diagnostic procedures and treatment for all citizens. Almost all citizens (>98%) are registered with a GP, who acts as gatekeeper to the rest of the health care system (except for emergencies and private practicing otorhinolaryngologists and ophthalmologist who can be accessed directly) [29].

The Danish CPPs, introduced by national law in 2007 and implemented throughout 2008 and 2009, are guidelines listing specific criteria for urgent referral and descriptions of diagnostic sequences until treatment with specific maximum time frames [8].

2.2. Patient population and data collection

Identification of patients, data collection and drop-out analysis have been described in detail elsewhere [16,28]. In brief, patients were identified in hospital registers before (1 September 2004–31 August 2005) and in the Danish National Patient Registry after (1 May–31 August 2010) CPP implementation. Patients were eligible if they were 18 years or older, were listed with a GP, attended general practice as part of their diagnostic route and were registered with a verified first-time diagnosis of cancer with ICD-10 codes C01-C99, except C44.

A questionnaire was sent to each patient's GP. The GPs were asked to provide a detailed description of the patient's diagnostic pathway based on the electronic medical record. Subsequently, the study population was restricted to the patients where general practice was involved in the cancer diagnosis based on the question: "Were you/your general practice involved in diagnosing the cancer?" [28].

The GPs responded for 8023 (77%) of the 10,412 eligible patients [28]. Patients with participating GPs were less likely to be males and had fewer missing data on tumour stage than the other patients (data not shown) [28]. Responding GPs reported to be involved in diagnosing cancer for 6155 (77%) of cases [16]. We excluded 247 (1.8%) of cases due to missing information on the diagnostic interval [16].

2.3. Defining exposure and outcome

The exposure of the study was CPP implementation status defined according to the sampling time for the sub-cohorts: 2004/05 = before and 2010 = after CPP implementation

The study outcome was death from all causes within one year of diagnosis. Information on death was retrieved from the Danish Civil Registration System. All patients were followed for one year after diagnosis or until death, whichever came first. The date of diagnosis was obtained from the Danish Cancer Registry [28,30].

To explore the possible effect of lead time caused by the faster diagnosis after introduction of CPPs, we advanced the date of diagnosis of the patients in the before CPP cohort to an earlier point in time without postponing the patient's time of death. To estimate the number of days required to advance the date of diagnosis, we used the quantile regression model used by Jensen et al. [16]. We calculated the sex-, age-, comorbidity-, income- and education-adjusted differences in the diagnostic interval between the before and after cohort at every percentile from the 5th percentile to the 95th percentile. We then used these estimates to advance the date of diagnosis for each percentile in the before cohort as follows:

1. Patients in the before cohort were ranked according to the length of their diagnostic interval
2. The date of diagnosis was advanced in time according to the sex-, age-, comorbidity-, income- and education-adjusted differences in diagnostic intervals as follows:
   a Patients ranked from the first observation to the 4th percentile; no advancement of date
   b Patients ranked from the 5th to the 95th percentile; advancement of date of diagnosis by the estimated difference in diagnostic interval at the percentile in question.
   c Patients ranked from the 96th to the 100th percentile; advancement of date of diagnosis by the estimated difference in diagnostic interval at 95th percentile.
3. Step 2 was repeated by using the lower and upper limits of the 95% confidence intervals that were calculated using the procedure used by Jensen et al. [16].

By this procedure, we formed a cohort referred to as the "before cohort with lead time" (BwLT cohort).

2.4. Analyses

All analyses were done for nine specific cancer types separately, other cancer types and all combined (total). The nine cancer types were colorectal (C18-C20), lung (C34), malignant melanoma (C43), female breast (C50), prostate (C61), head and neck (C01-C14, C30-C32, C462 & C73), upper gastrointestinal (upper GI) (C15-C17 & C22-C26), gynaecological (C51-C58) and urinary system cancer (C64-C68).

We estimated the survival function for both the before and after cohort using Kaplan-Meier analysis to obtain differences in absolute survival from before to after CPP implementation. The survival function for the BwLT cohort was also estimated using Kaplan-Meier analysis. Finally, the survival function was calculated for the BwLT cohort according to the upper and lower 95% confidence limits of differences in the diagnostic interval between the before and after cohort to assess the minimum and maximum possible effect of lead time on survival.

To explore how much of the survival difference from before to after CPP implementation could be ascribed to lead time caused by the more timely diagnosis achieved over the years, we calculated (in percentages) how much the survival differences attributable to lead time comprised of the observed absolute difference in survival across the years. More specifically, we calculated how much the difference between the BwLT cohort and the before cohort constituted of the absolute differences between the before cohort and the after cohort at 30-day, three-month and one-year follow-up by using the following formula:

$$\text{Percentages attributable to lead time} = \frac{(\textit{survival rate before CPP with lead time} - \textit{observed survival rate before CPP})}{(\textit{observed survival rate after CPP} - \textit{observed survival rate before CPP})} x100\%$$